SYNTHESIS OF ^{14}C-LABELED 3-{[1-ETHOXYCARBONYL-3-PHENYL-(1S)-PROPYL]AMINO} -2,3,4,5-TETRAHYDRO-2-OXO-1H-1-(3S)-BENZAZEPINE-1-ACETIC ACID HYDROCHLORIDE ([^{14}C]CGS 14824A)

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SUMMARY

The title compound, CGS 14824A, was synthesized with a ^{14}C-label in the azepine ring in 14 steps starting with 1-bromo-3-phenylpropane (1) and K^{14}CN in an overall yield of 1.31%. The reaction of 1 with K^{14}CN yielded the nitrile 2 which upon hydrolysis followed by ring closure gave α-tetralone-1-^{14}C (4). Bromination of 4 followed by oxime formation gave the bromo oxime 5, which upon Beckmann rearrangement by acid treatment yielded the ring expansion product 6. The bromine atom of 6 was then replaced by an azido group, and an acetic ester side chain was introduced at the nitrogen atom. Catalytic reduction of the azido compound 8 gave a mixture of epimeric amino esters which was resolved by salt formation with L-tartaric acid. The negatively rotating isomer was then reacted with 4-phenyl-2-oxo-butanoate in presence of sodium cyanoborohydride to give a mixture of diastereoisomers which were separated as their benzyl esters by chromatography. The major isomer was then converted to labeled CGS 14824A.

Key Words: [^{14}C]CGS 14824A, α-Tetralone-1-^{14}C, synthesis

INTRODUCTION

Inhibitors of angiotensin-converting enzyme (ACE) are a new class of orally active antihypertensive agents (1,2). The efficacy of two compounds in this class - captopril and enalapril - in the treatment of hypertension and congestive heart failure (3) has led to intense research for newer compounds with ACE-inhibiting properties. CGS 14824A is one such compound discovered in our Research Department (4). We have now prepared this compound labeled with ^{14}C by total synthesis for pharmacokinetic and metabolism studies. The synthesis of the labeled compound is described in this paper, and some of the pharmacokinetic studies are described in two papers to be published elsewhere.

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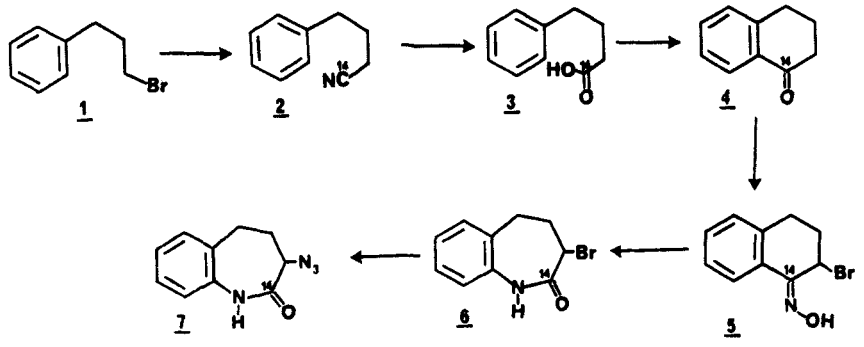
METHODS AND RESULTS

The first part of the synthesis which is outlined in Scheme I deals with the synthesis of carbonyl-labeled azido lactam 7, and the second part, outlined in Scheme II, deals with the synthesis of CGS 14824A from 7 by the addition of the two required side chains.

Scheme I

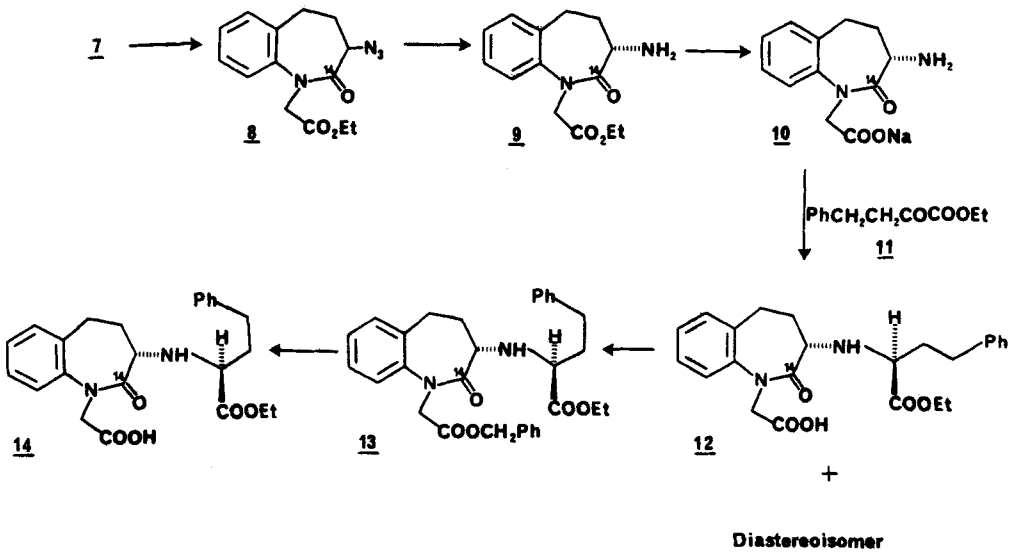


1 2 3 4 5 6 7

1-Bromo-3-phenylpropane (1) was reacted with $K^{14}CN$ to give the labeled nitrile 2 which was then hydrolyzed to the corresponding carboxylic acid 3. Cyclization of 3 by heating with polyphosphoric acid furnished α-tetralone-1-^{14}C (4). Bromination of 4 followed by reaction in situ with hydroxylamine produced the bromo oxime 5 which on heating with polyphosphoric acid underwent Beckmann rearrangement to yield the ring expansion product 6. The bromine atom of 6 was then replaced with an azido group by reaction with sodium azide to obtain the azido lactam 7.

An acetic ester side chain was then added by N-alkylation of the lactam 7 with ethyl bromoacetate in the presence of potassium hydroxide and tetrabutylammonium bromide in tetrahydrofuran under phase-transfer condition. The resulting azido ester 8 was reduced by catalytic hydrogenation to produce a mixture of two epimeric amino esters, which was resolved by salt formation with L-tartaric acid. The negatively rotating isomer 9 was hydrolyzed with sodium hydroxide, and the sodium salt of the carboxylic acid 10 was then reacted with 4-phenyl-2-oxo-butanoate (11) in the presence of sodium cyanoborohydride. The reaction product was a mixture of two diastereoisomers which

Scheme II



were separated as their monobenzyl esters by chromatography on a column of silica gel. The benzyl ester of the major isomer 13 was debenzylated by catalytic hydrogenation to produce CGS 14824 (14), which on reaction with hydrogen chloride gave its hydrochloride salt, CGS 14824A. The radiochemical yield of [^{14}C]CGS 14824A from K^{14}CN was 1.31%.

EXPERIMENTAL

All melting points were taken on a Kofler hot stage apparatus. Thin layer chromatography (TLC) was carried out on a 0.25 mm silica gel 60 F-254 plates. Potassium cyanide-^{14}C was purchased from New England Nuclear.

Benzenebutane[^{14}C]nitrile (2). A solution of 11.3 g of 1-bromo-3-phenylpropane (1) in 70 ml of ethanol was added dropwise to a solution of 3.57 g of K^{14}CN (400 mCi) in 23 ml of water with stirring. The mixture was heated under reflux for 4 hr. Ethanol was removed by distillation under reduced pressure and the residue was extracted with ether. The ether extract was dried with $MgSO_4$ and then evaporated to give 7.7 g (360 mCi) of an oil. TLC in ethyl acetate-petroleum ether (1/9, v/v) showed one UV spot, identical to that of authentic benzenebutanenitrile (Aldrich).

Benzenebutanoic acid-carboxyl-^{14}C (3). The above nitrile was mixed with 15.5 ml of acetic acid, 14.4 ml of water and 4.6 ml of concentrated sulfuric acid, and the mixture was heated under reflux for 16 hr. The mixture was cooled, diluted with water and extracted with ether. The ether solution was dried with $MgSO_4$ and evaporated. The residue was mixed with 25 ml of toluene and evaporated to dryness under reduced pressure to remove traces of acetic acid; yield, 7.4 g of an off-white solid (340 mCi). TLC of the solid in ethyl *acetate*-petroleum ether (15/85, v/v) showed one UV spot, identical to that of authentic benzenebutanoic acid (Aldrich).

α-Tetralone-1-^{14}C (4). Polyphosphoric acid (25 g) was heated to 90°C and then added to the above benzenebutanoic acid, preheated to 70°C. The mixture was then heated at 95°C for 15 min. After cooling to 60°C, the mixture was diluted with water, stirred and cooled to room temperature. The aqueous mixture was extracted with ether. The ether extract was washed with 2N NaOH solution, dried with $MgSO_4$, and evaporated to yield 6.2 g of an oil (320 mCi). TLC of the oil in ethyl acetate-petroleum ether (1/2, v/v) showed one UV spot, identical to that of authentic α-tetralone (Aldrich).

2-Bromo-3,4-dihydro-N-hydroxy-1(2H)-naphthalenimine-1-^{14}C (5). To a magnetically stirred solution of the above ketone 4 in 54 ml of methanol was added dropwise 2.3 ml of bromine in 30 min. The mixture was then stirred for 90 min and 7.8 g of hydroxylamine hydrochloride was added. Stirring was continued for 4 days at room temperature. The outside of the flask was covered with aluminum foil during this period to protect the reaction mixture from light. After 4 days, methanol was removed by distillation under reduced pressure, and 100 ml of water was added to the residue. The mixture was stirred for 1 hr and then extracted with ethyl acetate. The ethyl acetate extract was dried with $MgSO_4$ and evaporated to dryness. The residue was triturated with ether and the resulting solid was filtered; yield, 6.9 g. TLC of the solid in ethyl acetate-petroleum ether (1/4, v/v) showed one major radioactive spot, and two minor radioactive spots due to unreacted α-tetralone and 2-bromotetralone.

3-Bromo-1,3,4,5-tetrahydro-2H-1-benzazepine-2-oxo-2-^{14}C (6). The above material was added to 44 g of polyphosphoric acid heated to 95°C. The mixture

was stirred and heated at 95°C for 15 min. It was then cooled to 75°C, and 50 ml of water was added to it very carefully. The mixture was then extracted with chloroform. The chloroform extract was washed with Na_2CO_3 solution, dried with $MgSO_4$ and evaporated. The residue was stirred with petroleum ether and filtered to yield 3.5 g of a solid. The filtrate containing unreacted tetralone and bromotetralone was evaporated, and the residue was recycled to give 1.8 g of the product 6. The combined yield of 5.3 g having 168 mCi of radioactivity was 42% of theory based on $K^{14}CN$.

3-Azido-1,3,4,5-tetrahydro-2H-1-benzazepine-2-oxo-2-^{14}C (7). To a solution of 4 g (128 mCi) of the above solid in 40 ml of dimethylsulfoxide was added 1.65 g of sodium azide. The solution was heated at 80°C for 4 hr, and then cooled to room temperature and diluted with 100 ml of water. The precipitated solid was filtered and dried at 55°C/1 mm for 16 hr; yield, 3.37 g; m.p. 148 - 150°C, reported 142 - 145°C (4). The infrared spectrum showed bands at 1675 (C = O) and 2150 cm^{-1} (N_3).

Ethyl 3-azido-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-2-^{14}C-1-acetate (8). To a mixture of 3.37 g of the above compound 7, 0.56 g of tetrabutylammonium bromide, and 1.2 g of powdered KOH in 35 ml of tetrahydrofuran was added 2.2 ml of ethyl bromoacetate. The mixture was stirred vigorously at room temperature for 1.5 hr and filtered. The filtrate was evaporated under reduced pressure to give 4.6 g of an amber oil. TLC in ethyl acetate-petroleum ether (3/7, v/v) showed one UV spot different from that of 7. Infrared spectrum showed peaks at 1675 (lactam C = O), 1750 (ester C = O) and 2150 cm^{-1} (N_3).

Ethyl 3-amino-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-2-^{14}C-1-acetate (9). The above compound 8 (4.6 g) was dissolved in 50 ml of ethanol, and 250 mg of 10% palladium-on-charcoal was added to it. The mixture was shaken in an atmosphere of hydrogen for 3 hr with periodic venting to remove the nitrogen evolved in the reaction. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give 4.1 g of a yellow oil. The infrared spectrum showed the absence of the 2150 cm^{-1} peak due to the azido group. The above oil was dissolved in 10 ml of ethanol, and 2.51 g of L-tartaric acid was added to the solution. The mixture was heated with

further amounts (40 ml) of ethanol to obtain a clear solution which was then stirred at room temperature for 24 hr. The crystallized solid was collected by filtration. To the filtrate was added 2 g of pure L-tartrate salt of unlabeled compound 9. The mixture was heated to obtain a clear solution which was then stirred at room temperature for 24 hr. The crystallized solid was collected by filtration, washed with ethanol and mixed with the solid obtained after the first crystallization. The combined solid was crystallized once more from ethanol, m.p. 168 - 171°C indentical to that of authentic salt (4); yield, 3.9 g (43 mCi). The free base 9 was prepared from the salt by treatment with 10% NH_4OH followed by extraction with methylene chloride. Removal of the solvent yielded 2.47 g of pure 9; m.p. 107 - 108°C and $[\alpha]_D$ -288.7°, identical to those of authentic compound (4).

3-Amino-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-2-^{14}C-1-acetic acid sodium salt (10). To a solution of 0.5 g of sodium hydroxide in 35 ml of methanol and 0.5 ml of water was added 2.47 g of compound 9, and the solution was stirred at room temperature for 24 hr. Methanol was removed by distillation under reduced pressure and the residue was triturated with ether to give 2.41 g of the sodium salt 10 as a solid after drying in vacuum.

3-{[1-Ethoxycarbonyl-3-phenyl-(1S)-propyl]amino}-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-2-^{14}C-1-acetic acid (12) and the RS isomer. A solution of 2.41 g of 9 and 7.75 g of ethyl 2-oxo-4-phenylbutanoate (11) in 23 ml of acetic acid and 23 ml of methanol was stirred at room temperature for 3 hr. A solution of 0.9 g of sodium cyanoborohydride in 10 ml of methanol was then added dropwise to it during 3 hr. The mixture was stirred overnight at room temperature and then treated with 5 ml of 6N HCl. The solution was evaporated under reduced pressure and the residue dissolved in 2N NaOH. The basic solution was extracted with ether to remove unreacted 11. The aqueous part was then acidified with 6N HCl to pH 4 and extracted with ethyl acetate. The ethyl acetate extract was dried with $MgSO_4$ and evaporated to dryness. The residue was dried under high vacuum and then dissolved in ethyl acetate. The ethyl acetate solution was treated with ethereal hydrogen chloride and stirred overnight at room temperature. The solvents were removed to give a foamy

solid (3 g).

3-{[1-Ethoxycarbonyl-3-phenyl-(1S)-propyl]amino}-2,3,4,5-tetrahydro-2-oxo-1H-(3S)-benzazepine-2-^{14}C-1-acetic acid([^{14}C]CGS 14824) (14). The above solid was dissolved in 20 ml of methanol and the solution was neutralized with 20% cesium carbonate solution. The solution was then evaporated under reduced pressure and dried under high vacuum to obtain the cesium salt as a solid. The solid was suspended in 10 ml of dimethylformamide and treated with 1.7 g of benzyl bromide. The mixture was stirred at room temperature for 48 hr and then treated with 50 ml of water. The mixture was extracted with ethyl acetate. The ethyl acetate extract was dried with $MgSO_4$ and evaporated to give an oily residue.

The oil was chromatographed on a column of silica gel using a mixture of ethyl acetate and petroleum ether (1/9, v/v) as the eluent. Two radioactive fractions were obtained. The major fraction (0.6 g) contained 5.3 mCi of radioactivity. This material was then dissolved in 20 ml of ethanol and 30 mg of 10% palladium-on-charcoal was added to the solution. The mixture was shaken in an atmosphere of hydrogen for 6 hr. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give a solid, m.p. 123 - 125°C, identical to that of authentic CGS 14824, prepared from authentic CGS 14824A. TLC of the radioactive compound in acetic acid-ethyl acetate (5/95, v/v) was identical to that of the unlabeled compound.

3-{[1-Ethoxycarbonyl-3-phenyl-(1S)-propyl]amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-2-^{14}C-1-acetic acid hydrochloride ([^{14}C]CGS 14824A). The above solid was dissolved in 10 ml of ethyl acetate, and 5 ml of ether saturated with hydrogen chloride was added to it. The mixture was stirred at room temperature for 2 hr and then cooled overnight at -5°C. The crystallized solid was collected by filtration and recrystallized from chloroform to yield 355 mg of a white solid (4.01 mCi); m.p. 182 - 185°C and $[\alpha]_D$ -140.6° which were identical to those of authentic CGS 14824A (4). The radiochemical yield (4.01 mCi) from the bromolactam 6 (128 mCi) was 3.13%. TLC of the radioactive compound in ethyl acetate-methanol-NH_4OH (8/2/1.5, v/v/v) showed only one UV spot identical to that of authentic CGS 14824A. Radioscan of the above chrom-

atogram showed only one peak containing more than 98% of the radioactivity in the sample.

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